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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,692	07/15/2004	Richard Smith-Carliss	END-04-1182PCT-US	4419

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EXAMINER	
SUTTON, DARRYL C	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,692	SMITH-CARLISS ET AL.	
	Examiner	Art Unit	
	DARRYL C. SUTTON	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-26 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Appeal Brief filed 12/16/2008. Examination has been reopened since the current examiner agrees with the arguments presented in the Brief. No new claims have been added.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 33 and 34 have been renumbered 31 and 32.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 recites the limitation "said analogs" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-26, 28, 29, 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by de Vos et al. (Eur. J. Pharmacol., 1995).

de Vos et al. teach that methadone maintenance therapy, MMT, is comprised of administering the inorganic acid addition salt of methadone, i.e. methadone HCl (Abstract). The formation and deposition of the major metabolite of methadone, EDDP in plasma was studied in 20 opiate addicts (title, page 361, 2nd column, 2nd paragraph). After administration of methadone HCl, blood samples of test subjects were taken (page 362, 2nd column, 1st paragraph). Plasma from healthy volunteers was spiked with EDDP $HClO_4$ over a concentration range of 5-800 ng/mL (page 362, 2nd column, 2nd paragraph), i.e. the perchloric acid inorganic acid addition salt of EDDP. Considering

the continuous presence of EDDP in long-term methadone addicts and the close chemical resemblance with methadone, it would be worthwhile submitting EDDP to further pharmacodynamic investigations (page 364, 2nd column, 2nd paragraph).

The prior art anticipates the instant claims insofar as it discloses a pharmaceutically acceptable agent, i.e. blood plasma, and EDDP, a compound of formula II. The physiological action of EDDP to block the α3β4 nAChR receptor and induce analgesia and/or deter abuse of abusive substances is due to its structure and therefore, it would be an inherent characteristic of the composition of the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over de Vos et al. (Eur. J. Pharmacol., 1995).

de Vos et al. is discussed above.

de Vos et al. do not teach a inorganic acid addition salt selected from the group consisting of hydrochloride, hydrobromide, sulfate, phosphate and nitrate.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the composition of de Vos et al. to use the hydrochloride salt of EDDP since methadone and EDDP have a close chemical resemblance and the hydrochloride

salt of methadone is pharmaceutically acceptable as taught by de Vos et al. One of skill in the art would reasonably understand that the hydrochloride salt of EDDP would also be pharmaceutically acceptable.

Claims 23-26 and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pohland et al. (J. of Med. Chem., 1971) in view of Gunaratna (Current Separations, 2000).

Pohland et al. teaches metabolites of methadone in man and rats (Abstract). 2-ethylidene-1,5-dimthyl-3,3-diphenylpyrrolidone, EDDP, is one of the metabolites which is produced by N-demethylation of methadone (page 194, 3rd paragraph – 2nd column, 1st paragraph).

Pohland et al. do not teach a pharmaceutical composition comprised of a pharmaceutically acceptable agent and EDDP.

Gunaratna teaches that knowledge of the toxic potential of lead drugs and their possible metabolites is essential for successful drug discovery (page 17, 3rd column, 2nd paragraph). The major site of metabolism in the body is the liver. Metabolism is comprised of Phase I pathways in liver microsomes where the drug is functionalized. A common reaction involved in Phase I is N-dealkylation, which is sufficient to make a drug more soluble, facilitating elimination. The various possibilities of the outcome of drug metabolism include producing a toxic metabolite, an active metabolite, an inactive metabolite or a reversible metabolite. The functionalization in the kidneys often results in compounds forming active metabolites which can enhance, modify, or inhibit the

desirable activity of the drug; sometimes the active metabolite initiates the pharmacological activity (page 20, 3rd column, 2nd and 3rd paragraphs, Figure F4). While there are many examples of both the parent and metabolite having the same pharmacological activity, some will show different pharmacological activity from the parent (page 21, 1st column, 2nd paragraph). Knowledge of metabolic pathways, metabolite stability and toxicity are important information in the drug development process and in the planning of human studies. Metabolite profiles are important for designing pharmacologically active metabolites and for selecting the right animal species for toxicology studies (page 21, 3rd column, 2nd paragraph).

Gunaratna does not teach a pharmaceutical composition comprised of a pharmaceutically acceptable agent and EDDP.

At the time of the invention, it would have been obvious to test the metabolites of Pohland et al. to see whether they were active metabolites which would enhance, modify, or inhibit the desired activities of methadone; or to determine whether the EDDP shows the same or different pharmacological activity as methadone since methadone undergoes N-dealkylation, i.e. N-demethylation, which forms active metabolites of some drugs; and since this is standard practice in drug development as taught by Gunaratna. It would reasonably be assumed that the studies of metabolite activity, stability and/or toxicology would be comprised of formulations of the EDDP metabolite and pharmaceutically acceptable agents, such as buffers or solvents since they are to be carried out in animals; further, the studies would involve varying the amounts of EDDP to determine the activity and toxicity of the metabolite.

All claims are rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Darryl C. Sutton whose telephone number is (571)270-3286. The examiner can normally be reached on M-Th from 7:30AM to 5:00PM EST or on Fr from 7:30AM to 4:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached at (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Darryl C Sutton/

Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612